

## **The Enhancing Drug Safety and Innovation Act of 2006**

The Enzi-Kennedy legislation contains four titles: drug safety; establishment of the Reagan-Udall Institute for Applied Biomedical Research; clinical trials registry and results databases; and reform of conflicts of interests on FDA advisory committees. These provisions are outlined below.

### **Drug Safety**

It is not possible to know everything about a drug at the time of approval. Requiring sponsors to obtain all safety information before allowing the drug on the market would unduly delay patient access to new therapies. Pre-approval planning of how sponsors and FDA will identify, assess and manage risks post-approval is a more efficient way to obtain safety information, without compromising access.

FDA has post-approval authorities now, but they are not always the ideal tools to do what is needed. For example, if the agency believes a labeling change is necessary, it can request that the product sponsor make the change. If the product sponsor does not agree to the change, the agency cannot order the labeling change. FDA may initiate a misbranding action in the courts, but a sponsor who disagrees about a labeling change will contest the litigation, which can take months or even years to resolve. Moreover, such enforcement actions—seizing the product, or enjoining its distribution once FDA proves misbranding in court—may ultimately remove the drug from patients' hands.

Ideally, the agency and the sponsor will agree about how to address a safety concern. However, there is currently no clear way to conclude negotiations and move forward to action when there is disagreement.

### **Risk Evaluation and Mitigation Strategy (REMS)**

Under the Enhancing Drug Safety and Innovation Act, FDA would approve drugs (including biologic drugs) with risk evaluation and mitigation strategies (REMS). The sponsor and FDA will review the REMS at least annually for three years, as well as in applications for a new indication, when the sponsor suggests changes, or when FDA requests a review. Sponsors would propose a REMS and FDA would approve it after structured negotiations. The REMS is designed to be an integrated, flexible mechanism to acquire and adapt to new safety information about a drug.

#### **Minimal Elements of a REMS:**

A REMS would be required for approval of a new drug or new indication for an approved drug, and would have at a minimum the following:

- FDA-approved professional labeling;
- 15-day, quarterly, and annual reports of adverse events;

- A surveillance plan to assess known serious risks and to identify unexpected serious risks;
- A timetable for periodic assessment of the REMS.

### **Additional Elements:**

Based on the nature and magnitude of the safety issues with the particular drugs, additional elements of a drug's REMS may include one or more of the following:

- Sponsor-developed patient materials (distributed voluntarily);
- Required distribution of a Medication Guide when the drug is dispensed;
- A communication plan to physicians regarding other elements of the REMS;
- A black box warning in labeling about a known, serious risk;
- Post-approval registries, epidemiological studies, or clinical trials to assess empirical signals of serious risks or to screen for serious risks in expanded populations;
- Subject to a determination by the Secretary for a particular drug that such measures are necessary pre-clearance of, or specific disclosures in, advertising, and/or a prohibition on DTC advertisements for no more than 2 years after approval;
- Restrictions on product use or distribution to address a specific known serious risk (what is currently known as a RiskMAP).

### **Timeframes:**

Assessment, FDA review, and discussion of a REMS would take place with the following timelines:

- In the context of an application or supplement, FDA must begin to discuss the proposed REMS with the sponsor at least 60 days before the drug user fee action deadline to ensure time for thorough review of the REMS and to minimize the chance that dispute resolution, if invoked, would delay regulatory action;
- If there is new safety information about a serious risk, FDA may order the sponsor to submit an assessment of a REMS and must begin discussions within a set time period;
- A sponsor may submit an assessment of, and propose modifications (which may include reductions) to, a REMS at any time.

### **Dispute Resolution:**

When there is disagreement between FDA and the sponsor, the sponsor may initiate a structured dispute resolution process. This process brings fairness, timeliness and finality to the response to new safety information.

- This process begins by the sponsor proposing a REMS or assessing whether changes to an existing REMS are needed, and can be terminated by FDA and the sponsor reaching agreement at any point before issuance of an order;

- Once FDA/sponsor discussions of sponsor's proposed REMS begin, the sponsor may request review by the Drug Safety Oversight Board from day 20 until day 45;
- Both the sponsor's proposed REMS and FDA's alternative go to the next meeting of the Drug Safety Oversight Board for review;
- The Drug Safety Oversight Board reviews both proposals and makes recommendations to the Secretary within 5 days;
- The Secretary issues a final order within 7 days of receiving the recommendations.
- From the time FDA/sponsor discussions begin, the dispute resolution process takes from 46 days to 99 days, depending on circumstances.

### **Compliance and enforcement:**

A REMS requirement that is not working can, and should, be modified through the assessment process. Should a sponsor fail to comply with a REMS requirement, however, FDA can enforce the requirement as follows:

- Non-compliance with an element of a REMS would be a prohibited act;
- Civil money penalties could be imposed for knowing violation of any REMS component.

### **Application to generic drugs:**

A generic drug would be required to meet each element of a REMS except post-approval clinical trial requirements.

### **Resources:**

Increased drug user fees would be used to review REMS proposals and assessments and for FDA's general drug safety surveillance.

## **Reagan-Udall Institute for Applied Biomedical Research**

Title II of the Enhancing Drug Safety and Innovation Act would establish a new public-private partnership at the FDA to advance the Critical Path Initiative and improve the sciences of developing, manufacturing, and evaluating the safety and effectiveness of drugs, devices, and diagnostics.

The development of tools to evaluate drugs has not kept pace with developments in basic science and drug discovery. New tools are needed to better predict safety and efficacy. In order to increase the speed and efficiency of applied biomedical research leading to safe and effective therapeutic products, we need to create a new generation of performance standards and predictive tools that will provide faster and more certain answers about the safety and effectiveness of products in development. This has enormous potential to speed drug development without compromising safety, and in fact may enhance safety.

This public-private partnership, known as the Reagan-Udall Institute for Applied Biomedical Research, will facilitate these improvements in drug and device sciences by coordinating research activities between the regulators at the FDA and academic and industry researchers.

### **Activities of the Institute:**

- The Institute would identify and pursue research priorities to aid in the modernization of medical product development and enhancement of product safety so that research findings are quickly incorporated into regulatory regimes.
- The Institute would coordinate and expand existing government research and development programs and award grants and establish collaborations to carry out research priorities.
- The Institute would broadly distribute the knowledge and intellectual property developed through this research to ensure that the fruits of the research are incorporated into the product development and evaluation processes.
- The Institute would sponsor scientific conferences or symposia to assist in the evaluation of the safety of therapeutic products.

### **Governance Structure of the Institute:**

The Institute would be supported initially by Federal funds, and then by a combination of Federal funds and contributions from the pharmaceutical and device industries and philanthropic organizations.

- The Institute would have a Board of Directors comprised of:
  - Government officials;
  - Pharmaceutical and device industry researchers;
  - Academic researchers; and
  - Patient representatives.
- The Board of Directors would:
  - establish by-laws to carry out Institute activities;
  - award contracts and peer-reviewed grants;
  - select an Executive Director to oversee the day-to-day operations of the Institute; and
  - report to Congress annually on the support and operations of the Institute.

### **Clinical Trials Registry and Clinical Trials Results Database**

Clinical trials are a critical part of drug development. However, issues such as patient recruitment and timely access to information add complexity and cost to trials. The current NIH database, ClinicalTrials.gov, is a listing of trials for serious and life-threatening conditions, so that patients can learn more about these trials and register to

participate. However, not all clinical trials are required to register, and information about trial results important to providers and patients, particularly negative results, may or may not be released by sponsors. A central clearinghouse for information about clinical trials and their results would help patients, providers and researchers.

### **Clinical Trials Registry:**

Title III of the Enhancing Drug Safety and Innovation Act would establish a publicly available database at NIH to help enhance patient enrollment in clinical trials of drugs for any disease or condition and provide a mechanism to track subsequent progress of trials. This database would replace ClinicalTrials.gov, which would cease operations but remain publicly accessible.

- Late Phase II, Phase III, and Phase IV clinical trials would be required to register.
- Basic, searchable pieces of information about the trial would be required to be placed in fields in the database entry, while the bulk of the information about the trial would be in a narrative summary document. Information must be truthful, not misleading, and non-promotional.
- The information would be submitted after a trial is cleared by the Institutional Review Board (IRB) but before patients enroll.

### **Clinical Trials Results Database:**

Title III would also establish a publicly available database to ensure that results of trials are made public, and that patients and providers have the most up-to-date information.

- Results of all Phase III and Phase IV clinical trials would be required to be submitted to the database. There would be a process instituted to determine whether and how to require submission of the results of late Phase II trials, since these results may be commercially sensitive information.
- Like the registry, certain basic pieces of information would be placed in searchable fields in the database, while the bulk of the information would be in two summary documents (lay and technical). Both summary documents would be publicly available.
- Results would be submitted to the database after conclusion of data analysis. If regulatory action or publication is pending, the results would not be publicly available until that is resolved, which would protect both commercially valuable trial results and the ability of researchers to publish their results. The submitted results must be truthful, not misleading, and non-promotional. This would be assured via audits.

## **Compliance:**

- There are a variety of tools to enforce compliance with the registry and results database requirements:
  - Submission to the registry database would be a requirement for an investigational new drug exemption;
  - Unless information for a trial of a drug is submitted to the both the registry and results databases, FDA would not be permitted to file an application for approval of the drug, and the application would not be reviewed;
  - If a clinical trial is funded from NIH or another Federal agency, but the trial is not registered or the results are not submitted, the grant money would not be released;
  - Medical journals would be able to query the database to determine whether or not results had been submitted, since many journals require submission of results to a database for publication; and
  - Failure to submit required information, or the submission of false, misleading or promotional information would be a prohibited act under the Federal Food, Drug, and Cosmetic Act.

## **Effect on other laws:**

- State clinical trial databases would be preempted, and compliance with data submission requirements could not be used as evidence of off-label promotion of the drug.

## **Conflicts of Interest and FDA Advisory Committees**

Title IV of the Enhancing Drug Safety and Innovation Act would make improvements to FDA's process for screening advisory committee members for financial conflicts of interest. FDA relies upon its 30 advisory committees to provide independent expert advice, lend credibility to the product review process and inform consumers of trends in product development. Advisory Committee recommendations are non-binding on the agency, but the recommendations are usually followed.

Recently, questions have been raised about conflicts of interest that panel members on FDA Advisory Committees may have because of industry funding or other financial interests. When a conflict is identified, FDA considers whether the person's expertise is essential and whether the need for that person's service outweighs the risks of the potential for a conflict. Based on that evaluation, FDA has the statutory authority to grant a waiver and allow that person to serve.

Current FDA guidance on how to implement that authority contains inconsistent requirements that make it difficult to predict whether an individual under consideration will emerge as eligible for service, eligible only with a waiver, or recused. A lack of

transparency and predictability in how potential conflicts will be reviewed endangers the integrity of the review process. Finally, FDA faces a key challenge in identifying a sufficient number of people with the necessary expertise and a minimum of potential conflicts of interest to serve on advisory committees.

**Evaluation of candidates for appointment:**

- New candidates for appointment to advisory panels would be screened by FDA with the goal of minimizing potential conflicts of interest.
- FDA would be directed to enhance public nomination of individuals for service on advisory committees in order to expand the pool of qualified candidates.

**Evaluation of panel members for service at a meeting:**

- The categories of financial involvements used to evaluate a panel member for service at a panel meeting would be streamlined and clarified.
- FDA would be directed to define how interests imputed to an individual (such as financial interests of an employer) bear on eligibility for service on an advisory committee.
- FDA would be directed to standardize how individuals are evaluated for service on advisory committees across the centers of the agency.

**Disclosure of information:**

- The identity of panel members recused from service or who receive a waiver for service at an advisory committee meeting would be disclosed prior to a meeting.
- All financial involvements of panel members at a meeting would be required to be read into the public record of advisory committee meetings.

**Review of past panel members:**

- The HHS Inspector General would be directed to periodically review the current activities of past advisory committee members to ensure that individuals are not rewarded for their past votes as members of an advisory committee.